Accuracy of bleeding scores for patients presenting with myocardial infarction: a meta-analysis of 9 studies and 13 759 patients

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Postep Kardiol Inter 2015; 11, 3 (41): 182–190
DOI: 10.5114/pwki.2015.54011

A b s t r a c t

Introduction: Due to its negative impact on prognosis, a clear assessment of bleeding risk for patients presenting with acute coronary syndrome (ACS) remains crucial. Different risk scores have been proposed and compared, although with inconsistent results.

Aim: We performed a meta-analysis to evaluate the accuracy of different bleeding risk scores for ACS patients.

Material and methods: All studies externally validating risk scores for bleeding for patients presenting with ACS were included in the present review. Accuracy of risk scores for external validation cohorts to predict major bleeding in patients with ACS was the primary end point. Sensitivity analysis was performed according to clinical presentation (ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI)).

Results: Nine studies and 13 759 patients were included. CRUSADE, ACUITY, ACTION and GRACE were the scores externally validated. The rate of in-hospital major bleeding was 7.80% (5.5–9.2), 2.05% (1.5–3.0) being related to access and 2.70% (1.7–4.0) needing transfusions. When evaluating all ACS patients, ACTION, CRUSADE and ACUITY performed similarly (AUC 0.75: 0.72–0.79; 0.71: 0.64–0.80 and 0.71: 0.63–0.77 respectively) when compared to GRACE (0.66; 0.64–0.67, all confidence intervals 95%). When appraising only STEMI patients, all the scores performed similarly, while CRUSADE was the only one externally validated for NSTEMI. For ACTION and ACUITY, accuracy increased for radial access patients, while no differences were found for CRUSADE.

Conclusions: ACTION, CRUSADE and ACUITY perform similarly to predict risk of bleeding in ACS patients. The CRUSADE score is the only one externally validated for NSTEMI, while accuracy of the scores increased with radial access.

Key words: bleeding, acute coronary syndromes, risk scores.

Introduction

Percutaneous coronary intervention (PCI) has demonstrated a survival benefit over medical therapy in patients presenting with acute coronary syndromes (ACS). Consequently, indications have widened, including those with a relevant burden of comorbidities, from renal failure to advanced age [1–5].

Due to the increasing complexity of clinical presentation and despite continuous improvement in medical therapy and technologies, complications still affect a non-negligible number of patients, from acute kidney injury to peri-procedural myocardial infarction to bleeding [2, 5, 6]. The latter, especially, involves management of patients, in the cath lab, during subsequent hospitalization and also after discharge [7]. Major bleeding

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Received: 30.04.2015, **accepted:** 26.07.2015.

events have been clearly shown to negatively impact prognosis [7, 8], while minor bleeding may force patients to discontinue dual anti-platelet therapy, with a direct increased risk of stent thrombosis [9, 10].

A clear assessment of bleeding risk in ACS patients has become crucial to drive selection of stents in the cath lab and of antithrombotic drugs during hospitalization and after discharge. Age, hypertension, renal disease and use of oral anticoagulation therapy (OAT) have been commonly related to bleeding [11–13]. Clinical consideration, although obviously the first step, was demonstrated to be not sufficiently accurate, due to variability in clinician experience and to the different weight related to each factor [14].

At the same time, various clinical scores have been derived and externally validated, to appropriately depict

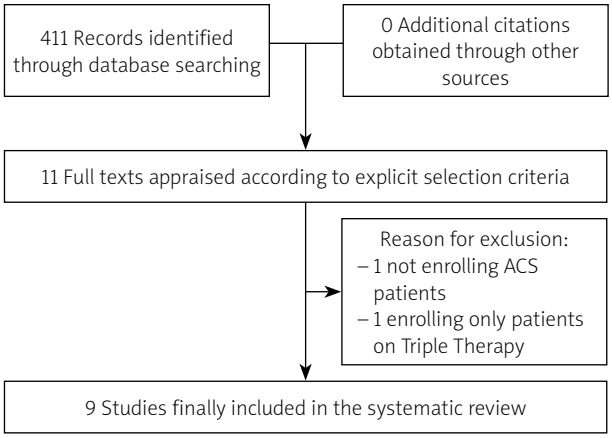

Figure 1. Flow chart

Table I. Baseline features of included studies

Studies	Number of patients	Area	Design of study	Number of centers
Ariza-Sole, 14	2036	Europe	Prospective	1
Abu-Assi, 13	4500	Europe	Retrospective	1
Ariza-Sole, 13	1064	Europe	Prospective	1
Amador, 11	516	South America	Prospective	1
Abu-Assi, 10	782	Europe	Retrospective	1
Chew, 11	1542	Australia, India, China, Russia	Prospective	58
Lopez-Cuenca, 13	273	Europe	Prospective	1
Nicolau, 13	1655	South America	Retrospective	1
Flores Rios, 12	1391	Europe	Prospective	1

Table II. Variables for risk scores

Variable	CRUSADE	ACUITY	ACTION	GRACE
Blood pressure	x		x	x
Heart rate	x		x	x
Diabetes mellitus	x		x	
Prior vascular disease	x			
Heart failure at presentation	x			
Gender	x	x	x	
Creatinine or clearance	x	x	x	xx
Baseline hematocrit/anemia	x	x	x	
Age		x	x	x
White blood cell count		x		
Clinical presentation		x		
Antithrombotic drug		x	x	
Weight			x	
Killip class				x

Table III. Baseline and interventional features of patients

Variable	Age [years]	Weight [kg]	Body mass index [kg/m²]	Female gender (%)	Hyper-tension (%)	Hyper-lipidemia (%)	Diabetes mellitus (%)	Renal disease (%)	Creatinine [mg/dl]	Oral anticoagulant therapy (%)	Unstable angina (%)	NSTEMI (%)	STEMI (%)	Radial access (%)	Drug eluting stent (%)
Ariza-Sole, 14		78	28	19	54	57	26	–	–	1.8	0	29	71	49	–
Abu-Assi, 13	69	76		28	–	–	28	Dyalisis (0.9)	1	6.3	0	67	33	83	–
Ariza-Sole, 13	62		27.8	21	53.8	53.5	23.8	–	–	–	0	0	100	59	–
Amador, 2011	69	73		32.2	75.3	57.4	35.3	–		–	0	100	0	–	–
Abu-Assi, 10	69	75		26	68	51	36	–	–	–	–	100	0	–	–
Chew, 11	60	85	–	22	60	63	31	–	–	–	0	70	30	–	–
Lopez-Cuenca, 13	75	78 ±12	29 ±4	32	78	55	47	21% (MDRD < 60 ml/min)	0.95 (0.83–1.13)	Previous to admission = 5.5% at discharge = 7.3%	30	70	0	61	45
Nicolau, 13	64			33	79	56	32	–	–	–	–	70	30	–	–
X Flores Rios, 12	64	79		21	48.5	40	19.2			2.6	0	0	100	81	–

the in-hospital bleeding risk of an ACS patient [11–13]. It remains unclear which of them is the most accurate, both in the overall setting of ACS and for patients presenting with ST segment elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction (NSTEMI).

Aim

Consequently we performed a meta-analysis to evaluate the accuracy of different bleeding risk scores for ACS patients.

Material and methods

The present paper is reported according to the PRISMA statement [15, 16].

Search strategy and inclusion/exclusion criteria

Two independent reviewers searched for pertinent articles in PubMed, Cochrane Collaboration and Google Scholar with the following query "((acute coronary syndrome) OR (ACS) OR (acute myocardial infarction) OR (MI) OR (unstable angina) OR (UA)) AND (risk score) AND (bleeding) NOT (review OR editorial OR letter)".

The following were the inclusion criteria (all had to be met): a) studies enrolling patients presenting with acute coronary syndromes; b) externally validating scores to predict bleeding after percutaneous coronary intervention. Exclusion criteria were (one was enough): a) not ACS patients; b) duplicate reporting (in this case the larger cohort was reported).

Clinical assessment of included studies

Age, weight, body mass index, cardiovascular risk factors, clinical presentation (unstable angina, NSTEMI and STEMI), and arterial access for PCI were appraised in each study by two blinded authors (Fabrizio D'Ascenzo; Giuseppe Biondi Zoccai). Moreover, rates and definitions of major bleeding, of bleeding related to access and of patients needing transfusions were appraised.

End points

Accuracy (defined as AUC, area under the curve) of risk scores in external validation cohorts to predict major bleeding in patients with ACS was the primary end point. Sensitivity analysis was performed according to clinical presentation (STEMI and NSTEMI).

Quality assessment of included studies

Design of study (prospective/retrospective), number of centers involved and geographical area were evaluated.

Statistical analysis

Continuous variables are reported as mean (standard deviation) or median (range). Categorical variables are

expressed as *n*/*N* (%). Statistical pooling was performed according to a random-effect model with generic inverse-variance weighting and computing AUC of the validation scores with 95% confidence intervals.

Using rate of events as the dependent variable, a random effect meta-regression was performed to test whether an interaction between baseline clinical features (age, gender, diabetes mellitus, NSTEMI or STEMI diagnosis, radial access) and accuracy was present, appraising major bleeding and stroke as outcomes. Moreover, impact of rates of bleeding on accuracy was tested, in order to understand the impact of reporting diagnosis.

Statistical analyses were performed with Comprehensive Metanalysis and Review Manager Revman 5.2.

Results

Four hundred eleven studies were first evaluated during research at the abstract level. Eleven articles were appraised as pertinent; two were excluded because of not evaluating ACS patients and including only patients on triple thrombotic therapy [17, 18]. Finally nine articles were included in the present review [19–27] (Figure 1).

Five of nine studies were developed in Europe, six were prospective and two were multicenter. CRUSADE, ACUITY, ACTION and GRACE [11–13, 28] were the scores externally validated (Tables I, II).

Mean age of included patients was 63 (59–64) years old, 23% (19–25) being female and 30% (28–34) presenting with diabetes mellitus. Seventy percent with STEMI (29–100), 30% with NSTEMI (0–71). Radial access was used the most 59% (49–81) (Table III).

The rate of in-hospital major bleeding was 7% (5–9.2), 1.03% (0.61–0.5) being related to access and 2.55% (2.01–2.95) needing transfusions (Table IV, Figure 2).

When evaluating all ACS patients, ACTION, CRUSADE and ACUITY performed similarly (AUC = 0.75: 0.72–0.79, I^2 = 91%; 0.71: 0.64–0.80, I^2 = 99%; and 0.71: 0.63–0.77, I^2 = 96% respectively) when compared to GRACE (0.66; 0.64–0.67, I^2 = 98%) (Figure 3).

When appraising only STEMI patients, all the scores performed similarly (Figure 4, all I^2 > 90%), while CRUSADE was the only one externally validated for NSTEMI.

In meta-regression analysis, age (B = 0.9, 95% CI; p = 0.45), diabetes mellitus (B = 0.21, 95% CI; p = 0.09),

Tables IV. Rates of adverse events during hospitalization

Variables	Major bleeding (%)	Patients needing transfusions (%)	Bleeding related to vascular access (%)	Recurrent ischemic events (%)
Ariza-Sole, 14	3.8	2.4		
Abu-Assi, 13	8.7	–	3	–
Ariza-Sole, 13	3.1	1	1.1	
Amador, 11	7	3	4	6.6
Abu-Assi, 10	9.5	4.7	–	–
Chew, 11	3.8	–	–	–
Lopez-Cuenca, 13	2.2	1.8	0.4	
Nicolau, 13	4.3	–	–	–
X Flores Rios, 12	9.8	–	0.5	–

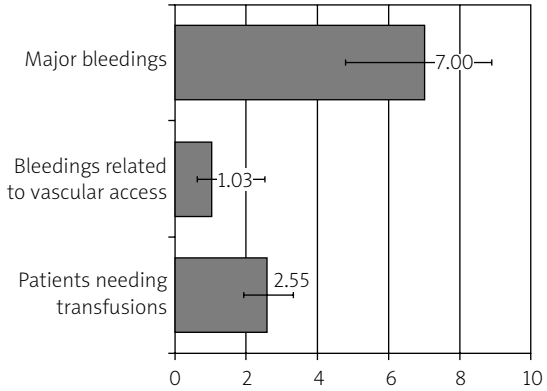

Figure 2. Rates of major bleeding events, of those related to vascular access and of patients needing transfusions

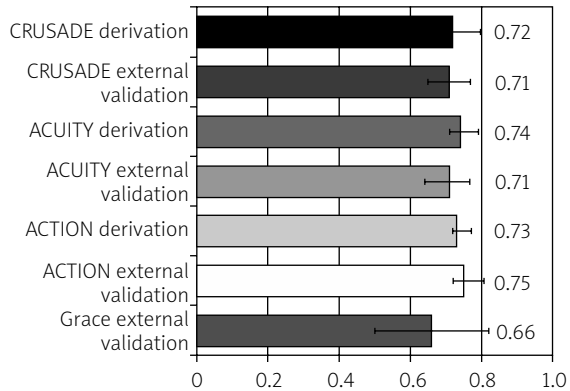

Figure 3. Accuracy of different scores (derivation and external validation) for all patients presenting with ACS

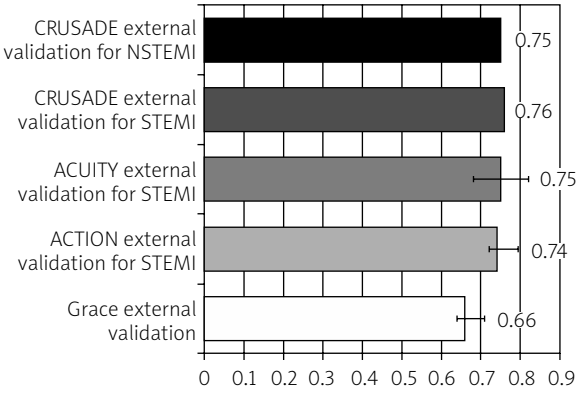

Figure 4. Accuracy of different scores for patients presenting with STEMI and NSTEMI

gender (B = 0.046, 95% CI; p = 0.21), NSTEMI (B = 0.5, 95% CI; p = 0.001), STEMI (B = 0.01, 95% CI; p = 0.27), and radial access (B = 0.01, 95% CI; p = 0.23) did not modify accuracy of CRUSADE.

Both for ACTION and ACUITY, accuracy increased with radial access (B = 0.5, 95% CI; p = 0.004, B = 0.5, 95% CI; p < 0.001) (Table V, Figure 5).

Rates of bleedings did not modify the accuracy of the tested scores.

Definition of major bleeding, as reported in Table VI, was consistent for all studies, apart from that of Nicolau *et al.* [17]; after excluding it, the accuracy of ACUITY was 0.70 (0.63–0.77, I^2 = 99%) without significant variation.

In funnel plot analysis (Figure 6), all the results were consistent among the studies.

Table V. Meta-regression results

Parameter	B	LCI	UCI	Value of *p*
		CRUSADE		
Age	0.9	–3.1	6.4	0.56
Gender	–0.04	–5.0	4.3	0.21
Diabetes mellitus	0.21	–0.26	2.7	0.09
STEMI	0.01	–0.34	0.51	0.28
NSTEMI	0.01	–0.24	0.56	0.39
Radial access	0.45	0.28	0.62	< 0.001
Rate of bleeding events	1.10	0.87	2.35	0.45
		ACTION		
Age	0.75	–4.5	9.9	0.98
Gender	–0.2	–8.1	5.6	0.45
Diabetes mellitus	1.24	–0.98	3.7	0.74
STEMI	1.02	–0.91	2.4	0.12
NSTEMI	0.24	–0.33	1.23	0.45
Radial access	0.50	0.26	0.95	0.04
Rate of bleeding events	2.81	0.56	4.51	0.65
		ACUITY		
Age	2.3	0.67	4.6	0.56
Gender	2.1	0.9	6.3	0.98
Diabetes mellitus	0.45	0.23	2.6	0.46
STEMI	0.79	0.56	2.7	0.87
NSTEMI	1.14	0.67	1.67	0.51
Radial access	0.50	0.17	0.71	< 0.001
Rate of bleeding events	0.78	0.56	1.99	0.67

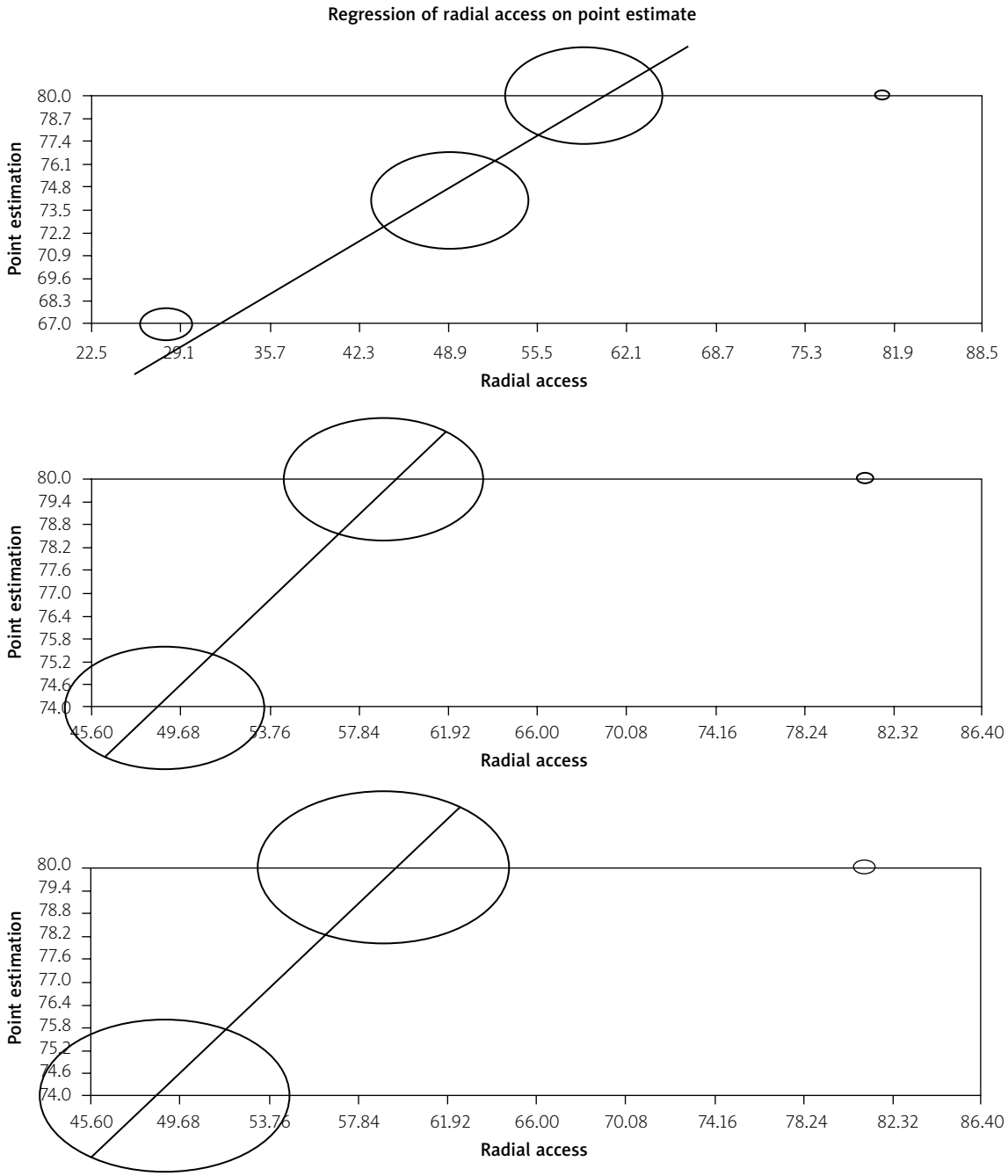

Figure 5. Meta-regression analysis for CRUSADE, ACTION and ACUITY (from above to below)

Discussion

The present paper represents a systematic review about the accuracy of three scores to predict risk of bleeding in patients with ACS, demonstrating that: a) age, gender, renal function and diabetes mellitus are the most frequently appraised predictors; b) all the scores offer similar accuracy; c) CRUSADE is the only score that is externally validated for NSTEMI; d) still larger sample sizes treated with a radial access are needed to validate bleeding scores.

Among all the risk scores, age, gender, renal function and diagnosis of diabetes mellitus are the most frequently appraised predictors. Increasing age and female gender have been widely described as related to periprocedural complications, among which bleeding events are the most frequent [1, 29, 30]. Similarly, pre-procedural reduced renal function has been widely related to bleeding, because of its association with several primary hemostatic disorders, in particular to a platelet malfunction due to a decrease of the release of adenosine triphosphate and the content of serotonin [31].

In ACS settings, CRUSADE, ACTION and ACUITY are the most accurate tools, showing an accuracy higher

Table VI. Definitions of bleeding

Variable	Clinical definition
Abu-Assi, 13	Intracranial bleeding, documented retroperitoneal bleed, hematocrit drop > 12% (baseline to nadir), any red blood cell transfusion when baseline hematocrit was < 28%, or any red blood cell transfusion when baseline hematocrit was < 28% with witness bleed
Ariza-Sole, 13	Intracranial or intraocular bleeding, access site hemorrhage that required intervention, reduction in hemoglobin of ≥ 4 g/dl without or ≥ 3 g/dl with an overt bleeding source, reoperation for bleeding, or blood transfusion
Amador, 11	Intracranial or intraocular bleeding, access site hemorrhage that required intervention, reduction in hemoglobin of ≥ 4 g/dl without or ≥ 3 g/dl with an overt bleeding source, reoperation for bleeding, or blood transfusion
Abu-Assi, 10	Intracranial or intraocular bleeding, access site hemorrhage that required intervention, reduction in hemoglobin of ≥ 4 g/dl without or ≥ 3 g/dl with an overt bleeding source, reoperation for bleeding, or blood transfusion
Chew, 11	Intracranial bleeding, documented retroperitoneal bleed, hematocrit drop > 12% (baseline to nadir), any red blood cell transfusion when baseline hematocrit was < 28%, or any red Blood cell transfusion when baseline hematocrit was < 28% with witness bleed
Lopez-Cuenca, 13	BARC definition: type 3a, overt bleeding plus hemoglobin drop of 3.5 g/dl, any transfusion with overt bleeding; type 3b, overt bleeding plus hemoglobin drop 5 g/dl, cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/ hemorrhoid), bleeding requiring *i.v.* vasoactive agents; type 3c, intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture, intraocular bleed compromising vision; type 4, coronary artery bypass graft (CABG)-related bleeding (perioperative intracranial bleeding within 48 h, reoperation after closure of sternotomy for the purpose of controlling bleeding, transfusion of 0.5 U whole blood or packed red blood cells within a 48-h period, chest tube output 0.2 l within a 24-h period); type 5, fatal bleeding (type 5a, probable; type 5b, definite)
Nicolau, 13	Any bleeding requiring specific action from the staff (surgery for pseudo aneurysm, transfusion or requiring a third party opinion)

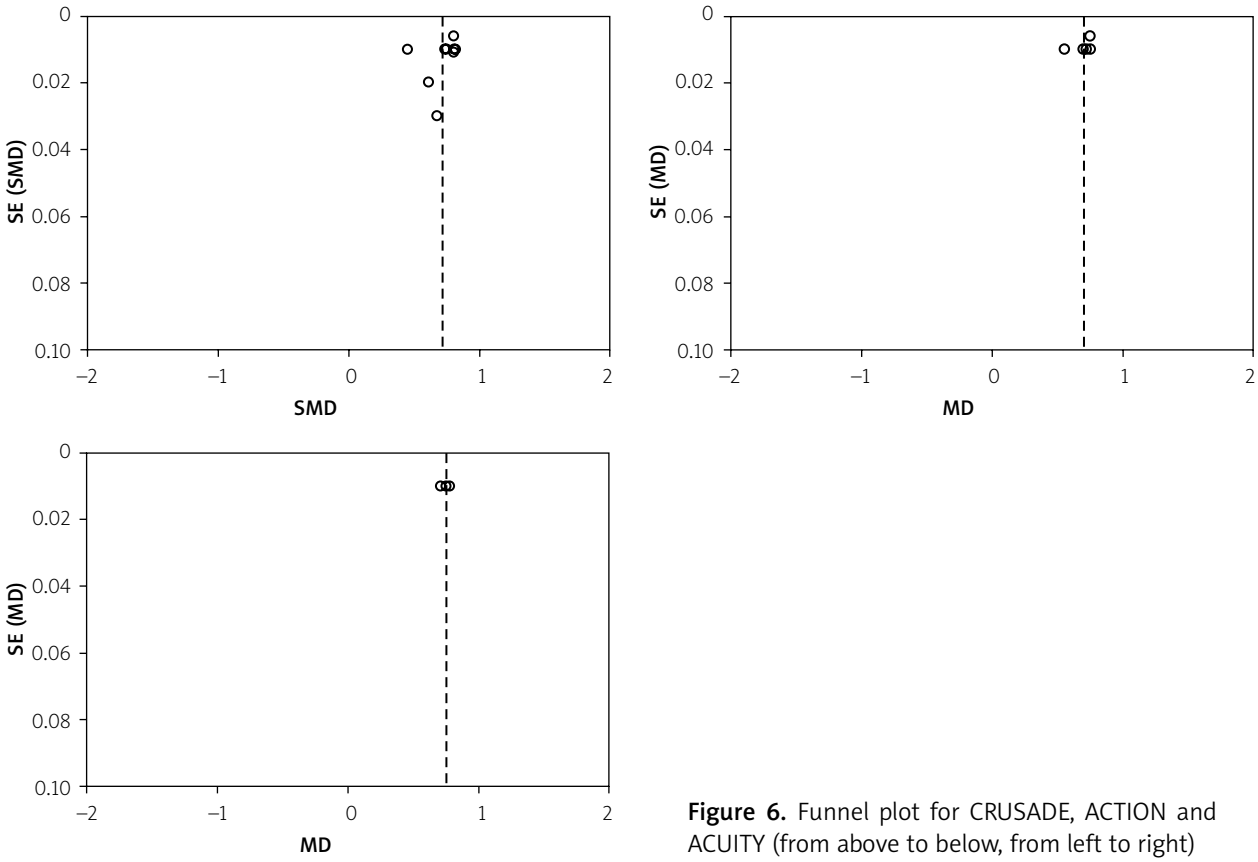

Figure 6. Funnel plot for CRUSADE, ACTION and ACUITY (from above to below, from left to right)

than 0.70, which is very similarly to the GRACE score, the most extensively validated and used score predicting risk of ischemic events in ACS [28]. This similar performance is probably related to evaluation of similar risk factors and clinical predictors of bleeding, although derived from samples of different size. The CRUSADE and the ACTION scores were derived from more than 70 000 patients, compared to about 20000 for ACUITY. ACUITY included

patients with unstable angina, NSTEMI and STEMI, while CRUSADE included only NSTEMI patients and ACTION included both STEMI and NSTEMI patients, consequently depicting a different population. Moreover, ACUITY was derived from patients included in two randomized controlled trials [32, 33] with pre-specified inclusion/exclusion criteria, while the other two studies were registries enrolling all consecutive patients.

These scores were derived from patients not treated with some contemporary drugs and strategies commonly used for patients with ACS. Apart from ACUITY, no data about bivalirudin have been reported, the latter being a drug showing a reduction in in-hospital bleeding. With regard to access site, contrasting data are reported. In the present meta-analysis, approach-related bleeding events represented only about 1% when compared to an overall rate of 7%. When compared to large randomized controlled trials comparing radial versus femoral access in STEMI patients [34–36], the lower incidence of access-related bleeding is confirmed, while in the present paper an overall higher rate of hemorrhages is present, probably due to inclusion also of NSTEMI patients, who usually present with higher rates of comorbidity [1, 3, 4]. It is important to note that CRUSADE was the only score externally validated in NSTEMI patients, while the other two were tested for all myocardial infarction or only STEMI.

The accuracy of the present scores increases with radial access. Radial access when compared to femoral access reduces arterial site bleeding. Consequently accuracy of scores is still used for the events not related to the site of access. The latter are more commonly related to clinical features and presentation, while access management is affected by different factors not embedded in the present score, such as experience of the operators [37].

The present work has several limitations. We considered only studies that had at least one analysis performed to assess incremental predictive ability. Many other articles reporting only risk factors without a clear evaluation of prediction were excluded, and it is important to remember that empirical evidence in other fields, for example cancer, suggests that new predictors are almost always significant. Moreover, patients with an indication for oral anticoagulation were excluded from the present study, thus limiting the potential usefulness of these scores in this population [38, 39]. Finally, meta-regression was tested on few studies.

Conclusions

ACTION, CRUSADE and ACUITY perform similarly to predict risk of bleeding in ACS patients. The CRUSADE score is the only one externally validated for NSTEMI, while accuracy of the scores increased with radial access.

Conflict of interest

The authors declare no conflict of interest.

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